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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,772	07/12/2001	Masahiro Iwamoto	46124-5001-01	1361

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EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	13

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/902,772	IWAMOTO ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5 and 20-39* is/are pending in the application.

4a) Of the above claim(s) *1,5,20-31,33,35 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *32,34 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The Response and Amendments filed July 15 2003 have been entered and considered. Claims 1, 5, and 20-39 are pending, Claims 1, 5, 20-31, 33, 35, and 39 are withdrawn from consideration as being drawn to non-elected subject matter, and Claims 32, 34, and 36-38 have been considered in this Office Action.

In the previous Office Action mailed 1-15-03, the indication of Claim 34 as objected to in the Form PTO-326 was made in error. There is no objection to Claim 34. The examiner apologizes for this mistake and any inconvenience it may have caused.

Rejections Withdrawn

The rejection of Claims 32 and 34 for double patenting over U.S. Patent No. 6,294,354 is withdrawn in light of Applicants argument and review of the restriction in the parent application.

The rejection of Claims 36-38 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn. The amendment of Claim 36 has changed the scope of part (b) of the claim to refer to any primer sequence that encodes a protein that has cell calcification inhibitory activity and increases DNA synthesizing ability of the cells. Thus, since the primer sequence is not limited to SEQ ID NO:4, it would be possible to use a primer comprising a nucleic acid sequence complementary to the

nucleotides spanning the "splice junction" at nucleotide 655 of SEQ ID NO:1 to amplify SEQ ID NO:1, for example, which encodes a protein containing amino acid insertions relative to SEQ ID NO:4.

Rejections Maintained/ New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32 and 34 and Claims 36-38 as amended are rejected under 35 U.S.C. 102(b) as being anticipated by Dhordain et al. (Mech. Dev. (1995) 50: 17-28; cited in IDS of Paper No. 6).

Dhordain et al. teach the cloning of the chicken erg gene (ck-erg) (see lines 6-7 of abstract). The erg gene composition of Dhordain et al. appears to be indistinguishable from the pharmaceutical compositions of present Claims 32 and 34. The erg gene disclosed in Dhordain et al. appears to have a sequence identical to SEQ ID NO: 1 and 3 of the present invention except that it contains an extra 81 nucleotides from position 655-735 of SEQ ID NO:1 (see sequence alignment attached to the previous Office Action, Paper No. 11).

Response to Arguments:

Applicants argue that the erg gene in Dhordain et al. was used to study its expression and not used as a pharmaceutical composition and that if the intended use of the claimed composition is considered in Enablement then it should be considered in the prior art. This argument has been considered but is not deemed persuasive. A claim containing a recitation with respect to the manner in which a claimed article is intended to be employed does not differentiate the claimed article from a prior art article if the prior art article teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987) (see MPEP 2114 and case law cited therein). In the present case, the claimed composition does not contain any components that patentably distinguish it from the composition of Dhordain et al. The examiner notes that intended use is considered for enablement of product claims because the Specification must teach how to make and *use* the product in order to meet the requirements for enablement.

Claims 36-38 have been added to this rejection due to the amendment of Claim 36 changing the limitation that the complementary nucleic acids a), b), and c) comprise the complement of nucleotides 645-662 of SEQ ID NO: 1 to comprise the complement of nucleotides that span the splice junction of nucleotide 655 of SEQ ID NO:1.

Dhordain et al. teaches a ^{35}S labeled (radioactively labeled probe) antisense RNA probe synthesized from chicken erg cDNA (p. 27, Col. 2, "In Situ Hybridization"). In addition, it appears that the probe of Dhordain et al. is the complement (antisense) of nucleotides that span the splice junction at nucleotide 655 of SEQ ID NO:1 (see sequence alignment attached to Paper No. 11). The probe of Dhordain et al. is capable

of identifying a nucleic acid encoding ck-erg (see Fig. 7); which inherently has cell calcification inhibitory activity. Therefore, Dhordain et al. meets the limitations of Claims 36, 37, and 38.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: the nature of the invention; the breadth of the claims; the predictability or unpredictability of the art ; the amount of direction or guidance presented; the presence or absence of working examples; the quantity of experimentation necessary; the state of the prior art; and, the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Breadth of the Claims

The claims are drawn to pharmaceutical compositions comprising genes. Thus, the claims encompass the intended use of the claimed compositions in gene therapy.

Nature of the Invention

A review of the Specification appears to indicate that the invention is the discovery of a "novel isoform of the c-erg gene (herein referred to as 'C-11 gene' or 'C11 gene') which is an erg gene derived from chicken" (p. 5, lines 1-5 of Specification).

The Amount of Direction or Guidance Presented and the Presence or Absence of Working examples:

The present Specification does not provide any working examples of methods of gene therapy using the disclosed nucleotide sequences and does not provide any guidance as to any protocols for using the disclosed sequences in any gene therapy methods.

State of the prior art and relative skill of those in the art

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by recently published reviews. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist

including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18:19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (Nature Reviews/Genetics 1: 9199, 11/2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

The predictability or unpredictability of the art

The art of gene therapy is highly unpredictable as evidenced by the problems discussed in the paragraph above.

In consideration of each of the above factors, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

The examiner notes that this enablement rejection can be overcome by deleting the term "pharmaceutical".

Response to Arguments:

Applicants argue that c-erg and C-11 inhibit calcification of osteoblasts in vitro and that one of skill in the art would consider the data from the in vitro osteoblast model as correlating to the functional cell calcification in vivo. Applicants provide three abstracts as evidence.

The examiner has considered this argument but does not deem it to be persuasive. The issue at hand is not whether the activities of the erg protein in vitro are representative of those activities in vivo but how to effectively deliver erg or C-11 DNA to a cell in order to get an effective response (e.g. in order to treat). The abstracts referred to on page 10, second paragraph of the Response filed July 15, 2003 do not describe models for effectively delivering erg or C-11 DNA for treatment of any diseases but only describe a model of in vitro maturation of osteoblasts (Gu et al.), a primary cell culture as a model of natural osteoblastic function (not a model for drug delivery; Collignon et al.), and a primary cell culture which might be appropriate for studying compounds that increase bone calcification (Ecsedi et al.). As discussed below, in order to use the erg or C-11 genes pharmaceutically they must be delivered effectively to the appropriate tissues. In this argument and in the submitted abstract, considerations of getting the gene to the appropriate location in the appropriate amounts have been omitted. This problem of gene delivery is what the references cited in the previous Office Action state is the problem with gene therapy.

Applicants also argue that it is well known that direct injection of naked nucleic acid molecules into muscle results in high levels of expression. Applicants refer to U.S. Patent No. 5,580,859 ('859 patent) as evidence for this argument. This argument has

been considered but is not persuasive. Unlike the present application, the '859 patent contains claims and detailed examples of methods of injecting naked DNA into mice. The '859 patent does not claim or provide examples of any practiced method of *treatment* by DNA injection. The present application only provides a suggestion that the DNA could be delivered for treatment of osteoarthritis and OPLL. The present Specification does not teach how the DNA would be delivered but only vaguely suggests to inject the DNA locally (this suggestion at page 14 of the Specification is unclear as to what is being administered, protein or DNA, since the Specification only refers to using "conventional" methods to administer the "pharmaceutical composition" and administration of DNA by any method was not considered "conventional" as evidenced by the references cited in the previous Office Action, Paper No. 11). The present Specification does not teach what kind of vector to use in the administration, how much of the DNA should be injected, where the DNA should be injected, or how much DNA expression would be necessary to treat the osteoarthritis or OPLL, for example. These factors are essential in using the erg gene or C-11 gene as a pharmaceutical composition and as evidenced by Nishikawa et al. (Human Gene Therapy (2001) 12: 861-870), choosing the appropriate steps in a method of direct DNA delivery is not routine. Nishikawa et al. indicate that the physicochemical properties of DNA-vector complex will affect its passage through capillaries, extravasation, capture by the mononuclear phagocytes, and uptake by target cells (see p. 862, Col. 1, 2nd paragraph). Moreover, the uptake of plasmid DNA by muscle cells is relatively inefficient (less than 1% of the injected dose), and is limited to cells adjacent

to the track of injection (see Nishikawa et al., p. 862, Col. 2, 1st paragraph). In addition, Nishikawa et al. states that there are many complex factors that influence the biodistribution of the administered DNA and therefore efficient and target-specific gene transfer is difficult to achieve (see p. 864, Col. 2, 2nd section). Finally, Nishikawa et al. states "The successful clinical application of nonviral vectors will rely on a better understanding of the barriers to gene transfer and on the development of vectors that can overcome such barriers" (p. 866, "Conclusions"). Thus, it appears that while Applicants in vitro model may represent the activity of the erg or C-11 genes in vivo in their natural state, the model and Specification do not provide sufficient information that would have allowed one of skill in the art to use the claimed pharmaceutical compositions in a method of gene therapy. As stated in the previous Office Action, the art of gene therapy is highly unpredictable and in the present case undue experimentation would be required to use the claimed compositions because of variability in prediction of the outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented.

Claim 36-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It appears that the specific nucleic acids claimed (those selected from the group of parts (a), (b), or (c) that comprise the complement of nucleotides 645-662 of SEQ ID

NO:1 (as previously claimed) or that comprise the complement of nucleotides that span the splice junction at nucleotide 655 of SEQ ID NO:1 constitute new matter. Claim 36 was added in the Second Preliminary Amendment filed September 6, 2001 and amended (to recite the complement of nucleotides that span the splice junction at nucleotide 655) in the Response and Amendment filed July 15, 2003. The Specification as originally presented does not appear to describe primers or probes comprising specifically the complement of nucleotides 645-662 of SEQ ID NO:1 or comprising specifically the complement of nucleotides that span the slice junction at nucleotide 655. Claims 37 and 38 are also rejected. Since the Specification as originally filed does not describe the primers and probes of Claim 36, it follows that the Specification does not describe those probes as being labeled as claimed in dependent Claims 37-38.

Response to Arguments:

Applicants argue that the Specification as originally filed contains support for probes specific for C-11 (SEQ ID NO:1) or c-erg (SEQ ID NO:3) at page 6, lines 21-26 and the position for excision in C-11 relative to c-erg at page 9, lines 21-24. Therefore, one of skill in the art would understand that probes specific to C-11 would include nucleotides spanning the excision or splice junction at nucleotide 655. This argument has been considered but is not deemed persuasive for the following reasons.

While Applicants have cited a broad and generic reference to probes to the c-erg and C-11 genes (p. 6, lines 21-26), Applicants have not shown that the original disclosure contained any explicit or implicit references to the specific species of probe claimed. Thus, Applicants have not pointed to how the original disclosure would lead

those of skill in the art to the specific species claimed. New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure (MPEP 706.03(o) and In re Wertheim, 191 USPQ 90 (CCPA 1976) cited therein; also see MPEP 2163.05(II)).

In the present case, the generic disclosure on page 6, lines 21-24 to a probe against a DNA sequence specific to the C-11 gene or c-erg gene does not constitute written description of the particular species of a nucleic acid complementary to nucleotides that span the splice junction at nucleotide 655 because the disclosure would not reasonably lead those skilled in the art to this specific species presently claimed. The Specification provides a broad and generic disclosure of probes specific to the C-11 gene or c-erg gene. The only three species of this genus that are described in the Specification are three probes, C11A, C11B, and C11C that amplify the entire coding region of c-erg (see p. 10 and p. 15, lines 12-14) and that do not appear to span the splice junction at nucleotide 655. The Specification does not expressly or implicitly describe probes that span the splice junction at nucleotide 655 of SEQ ID NO:1. Moreover, the Specification does not refer to a splice junction in SEQ ID NO:1. Thus, the rejection is maintained.

Conclusions

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
September 17, 2003

CHRISTOPHER S. F. LOW
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